n-3PUFA and Holter-derived autonomic variables in patients with heart failure: Data from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca (GISSI-HF) Holter substudy

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BACKGROUND n-3 Polyunsaturated fatty acid (n-3PUFA) supplementation in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca (GISSI-HF) study reduced total mortality in patients with heart failure (HF), but the mechanism of action is still debated. The hypothesis of the present GISSI-HF substudy was that n-3PUFA may have beneficial effects on cardiac autonomic control.

OBJECTIVE To evaluate the effect of 1 g/day of n-3PUFA vs placebo on heart rate variability variables, deceleration capacity, and turbulence slope.

METHODS The GISSI-HF study enrolled patients with HF of any cause and severity. Twenty-four-hour (range 16–24 hours) Holter recordings were performed and analyzed in 388 patients at baseline, 3 months, and 12 months. Baseline characteristics were compared by using the χ^2 test, *t* test, or nonparametric Wilcoxon 2-sample test. Changes over time were tested by using the analysis of covariance adjusted by baseline values.

RESULTS At baseline, 36% of the patients were older than 70 years, 82% were men, 92% presented a left ventricular ejection fraction <40%, and 80% were in New York Heart Association class II. An increase in mean RR interval, standard deviation of all normal-to-normal RR intervals, very low frequency power (all $P < .05$), and turbulence slope ($P = .05$) was observed after 3 months in the n-3PUFA group compared to the placebo group, independently of the frequency of dietary fish consumption or beta-blocker treatment. These differences between study groups were no longer statistically significant at 12 months. A per-protocol analysis in patients compliant with study treatment showed similar results.

CONCLUSIONS n-3PUFA supplementation partially restored autonomic modulation in patients with chronic HF; this effect was maximal after 3 months of treatment.

KEYWORDS Heart failure; Autonomic cardiac control; Holter recording; Heart rate variability; n-3PUFA; Clinical trial

ABBREVIATIONS **ACEi/ARB** = angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; **ANCOVA** = analysis of covariance; **BB** = beta-blocker; **DC** = deceleration capacity; **GISSI-HF** = Gruppo Italiano per lo Studio dell'Insufficienza cardiaca; **HF** = heart failure; **HFp** = high frequency power; **HR** = heart rate; **HRT** = heart rate turbulence; **HRV** = heart rate variability; **LFp** = low frequency power; **LV** = left ventricular; **MI** = myocardial infarction; **n-3PUFA** = n-3 polyunsaturated fatty acid; **PVC** = premature ventricular complex; **SDNN** = standard deviation of all normal-to-normal RR intervals; **VLFp** = very low frequency power; **TS** = turbulence slope

(Heart Rhythm 2013;10:226–232)

Introduction

Epidemiological and clinical evidence support the role of n-3 polyunsaturated fatty acids (n-3PUFAs) in the prevention and treatment of cardiovascular disease.[1,2] The results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca (GISSI-HF) trial have shown that 1 g/day of n-3PUFA reduced all-cause mortality and hospitalizations for cardiovascular reasons in patients with chronic symptomatic heart failure (HF).[3] Worsening of HF

The study was planned, conducted, and analyzed by the GISSI Group, which has full ownership of the data, in complete independence from SocietàProdottiAntibiotici, Pfizer, Sigma Tau, and AstraZeneca that concurred to fund the study. **Address reprint requests and correspondence:** Maria Teresa La Rovere, MD, Divisione di Cardiologia, Fondazione S. Maugeri, IRCCS, Istituto Scientifico di Montescano, 27040 Montescano, Pavia, Italy. E-mail address: mariateresa.larovere@fsm.it; mtlarovere@libero.it.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2012.10.035

and presumed arrhythmic death accounted for 62% of the end point events and were lower in n-3PUFA-treated patients than in the placebo group.[4] A post hoc analysis of another subgroup of GISSI-HF patients with implantable cardioverter-defibrillator showed a somewhat lower incidence of arrhythmic events in the n-3PUFA group,[5] though the results of different small studies published up to now are conflicting.[6] Established effects of n-3PUFA including improvement in cardiac function[7,8] and vascular function may contribute to the observed clinical benefits of fish oil in HF.

An impaired autonomic control of the heart plays an important role in the development and progression of HF. Abnormalities of autonomic markers, including heart rate variability (HRV) and baroreflex sensitivity in patients with HF, are closely related to the degree of neurohormonal activation and to the severity of clinical conditions and are predictors of death.[9,10]

Several studies have evaluated the effects of dietary intake or supplementation of n-3PUFAs on heart rate (HR)[11] and autonomic variables in normal subjects and in patients with coronary artery disease,[12–18] while only few small, randomized controlled studies have been published, to the best of our knowledge, in patients with cardiomyopathy and HF.[19,20]

The design of GISSI-HF included a Holter substudy to assess the effects of n-3PUFA compared to placebo on ventricular arrhythmias and Holter-derived autonomic variables. In this contemporary population of 388 patients with chronic HF, we measured mean RR interval, conventional time- and frequency-domain HRV, the deceleration capacity (DC) of HR (recently proposed as a measure of cardiac vagal modulation[21]), and heart rate turbulence (HRT; which describes the biphasic response of the sinus node to premature ventricular complexes [PVCs][22]). The HR turbulence slope (TS) has been regarded as an indirect index of baroreflex function.[23] In these patients, HRV and TS have recently been shown to improve predictive discrimination and risk classification when added to clinical variables.[24]

Methods

Patients

The GISSI-HF trial was a randomized double-blind, placebo-controlled trial that randomized to n-3PUFA or placebo 6975 patients with symptomatic HF (New York Heart Association class II-IV) irrespective of the cause and left ventricular (LV) ejection fraction. Primary end points were time to death, and time to death or admission to hospital for cardiovascular reasons.[3] Of the 6975 patients, 388 in sinus rhythm underwent 24-hour digital electrocardiographic recording at the time of enrollment and at 3 and 12 months after randomization. All patients provided written informed consent before being enrolled to the substudy that was approved by the local ethics committees of the 41 participating sites.

Holter recordings and analysis

Holter recordings were performed with a high-resolution (1000-Hz) digital 12-lead portable Holter monitoring system (Model H12+, Mortara Instruments, Milwaukee, WI). The recordings were transferred to the Holter Core Laboratory in Montescano blinded to patient characteristics and outcome data.

Each beat was first automatically labeled as normal or aberrant by the Holter analysis software and then carefully edited by an expert medical analyst. Annotated RR time series were translated from proprietary binary format to an open format and transferred to a personal computer by using a dedicated software (SuperECG, Mortara Industries, Milwaukee, WI).

RR time series were processed according to previously described criteria.[25] Mean RR interval, the standard deviation of all normal-to-normal RR intervals (SDNN), the power of the very low frequency band (VLF; 0.01–0.04 Hz), of the low frequency band (LF; 0.04–0.15 Hz), and of the high frequency band (HF; 0.15–0.40 Hz) were selected for analysis. Mean RR and SDNN were calculated on the entire 24-hour recording, while very low frequency power (VLFp), low frequency power (LFp), and high frequency power (HFp) were calculated on all 5-minute segments with $\leq 5\%$ ectopic beats and then averaged. Spectral analysis was performed by using the autoregressive method (Burg algorithm with spectral decomposition) and the spectral power computed summing all spectral components with their central frequency inside the very low, low and high frequency band, excluding components with $< 10\%$ of the overall power in the bands.

To be able to detect shifts in HRV parameters (that on long-term recordings may be affected by several sources of variability), only recordings with HRV data analyzable for at least 2 hours during nighttime (11:00 PM–06:00 AM) and 2 hours during daytime were considered eligible for the study. Moreover, to avoid the confounding effect of abnormal HR patterns,[26] visual inspection was applied on a random sample of 50 recordings showing SDNN values above the 75th percentile.

The computation of DC was based on a novel phase-rectified signal-averaging technique suitable for the study of quasiperiodic oscillations in noisy, nonstationary signals.[21] The technique, based on the definition of anchor points in the RR signal that are used to align (phase-rectify) the oscillatory fluctuations followed by an averaging of the surrounding of the anchor points, allows one to separately characterize deceleration and acceleration of HR related to autonomic modulation.

The TS, defined as the steepest slope of the linear regression line for each sequence of 5 consecutive normal intervals following a PVC within the first 15 sinus rhythm beats, was computed on the averaged tachogram, obtained after the alignment of RR interval sequences surrounding isolated PVCs according to published criteria.[22]

Statistical methods

Predefined primary end point of the present substudy was the effect of n-3PUFA on the frequency of premature ventricular contractions (≥ 30 PVCs/h); Holter-derived autonomic variables were secondary end points.

Baseline characteristics of randomized patients (n-3PUFA vs placebo) were compared by using the χ^2 test, t test, or nonparametric Wilcoxon 2-sample test as appropriate.